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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAMA, JOANNE	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/781,142	KYRKANIDES, STEPHANOS	
	Examiner	Art Unit	
	JOANNE HAMA	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13,14,16-74,76-83,87-132,134,135,138 and 142* is/are pending in the application.

4a) Of the above claim(s) *44-71,76-82 and 92-132* is/are withdrawn from consideration.

5)☒ Claim(s) *83* is/are allowed.

6)☒ Claim(s) *1-11,13,16-43,72-74,87-91,134 and 135* is/are rejected.

7)☒ Claim(s) *14,138 and 142* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/26/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 20, 2007 has been entered.

Claims 12, 15, 75, 84-86, 133, 136, 139-141, 143 are cancelled. Claims 44-71, 76-82, 92-132 are withdrawn. Claims 1, 72 are amended.

Claims 1-11, 13, 14, 16-43, 72-74, 83, 87-91, 134, 135, 138, 142 are under consideration.

Information Disclosure Statement

The information disclosure statement filed December 26, 2007 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Copies for C56, Dinchuk et al. 2003; C75 Goldgaber et al., 1989; C259 Stegenga et al., 1991; C293 Xu et al., 2000 are missing. Should Applicant wish to have these references considered, copies of them must be provided. Also with regard to the copies of the

abstract of NIH Grants (C187-C192), Applicant must provide a year for these references.

Withdrawn Rejections

35 USC § 112, 1st parag., Enablement

Applicant's arguments, see pages 13-21, filed December 20, 2007, with respect to the rejection of claims 1-43, 72-75, 83-91, 133-143 have been fully considered and are persuasive. Upon further consideration, the Examiner withdraws the Enablement rejection in favor of the 103 rejections, as described below. The rejection of claims 1-43, 72-75, 83-91, 133-143 has been withdrawn.

It is noted that Applicant has filed a 132 Declaration by Dr. Stephanos Kyrkanides. The Declaration has not been considered because it was not signed.

35 USC § 112, 1st parag., Written Description

Applicant's arguments, see pages 21-26, filed December 20, 2007, with respect to the rejection of claims 1-43, 72-75, 83-91, 133-143 have been fully considered and are persuasive. Upon further consideration, the Examiner withdraws the Written Description rejection in favor of the 103 rejections, as described below. The rejection of claims 1-43, 72-75, 83-91, 133-143 has been withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 6, 16-18, 25 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

While the specification and the art provides adequate written description for a CMV promoter and a beta-actin promoter, the specification does not provide guidance to arrive at a one that is a combination of the two. Claim 25 depends on claim 18 and the claim reads that the CMV promoter of claim 18 further comprises a beta-actin promoter. In the instant case, neither the art nor the specification teaches how to take regulatory regions of CMV and beta-actin and combine them to arrive at a functional, constitutive promoter. Because there is no guidance in arriving at this type of promoter, the claims lack written description.

Claims 1, 4, 6, 16-18, 25, 26, 29, 30, 87-89 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a composition comprising an isolated nucleic acid wherein the nucleic acid comprises a sequence encoding a HEX-alpha and a sequence encoding a Hex-beta, wherein the HEX-beta and HEX-alpha form a dimer and wherein the dimer can catabolize GM2 gangliosidase,

does not reasonably provide enablement for

a) said composition comprising a promoter, wherein the promoter is a CMV-beta-actin hybrid,

b) said composition producing a HEXB product which cross-corrects and catabolizes GM2 gangliosides,

c) said composition comprising a cell specific promoter as set forth in SEQ ID NO. 69.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 25 is readable such that one promoter sequence is comprised of a beta-actin promoter and CMV promoter sequence. Neither the art nor the specification provides any guidance as to what steps would be required such that an artisan would arrive at this hybrid promoter. For further discussion, see Written Description. As such, the claim is not enabled for this embodiment.

With regard to the claims being drawn to HEXB product cross correcting and catabolizes GM2 gangliosides (claims 29, 30), Chavany and Jendoubi, 1998, Molecular Medicine Today, 4: 158-165 teach that HexB is a homodimer of beta subunits and has similar substrate specificity to HexA with the key exception that it does not hydrolyze GM2. Because the art teaches that HexB does not hydrolyze GM2 and the specification does not provide guidance on making HexB that does hydrolyze GM2, the claims are not enabled for this aspect of the invention. It is noted that the specification does not

indicate what is meant by "cross correct" in claim 29. The Examiner has interpreted the phrase to mean that the HexB made in claim 26 (i.e. a beta homodimer) has the ability to replace the function of HexA (i.e., an alpha-beta heterodimer).

With regard to the search of SEQ ID NO. 69, nucleotides 1-1683 match the nucleotide sequence of rat NSE promoter. Nucleotides 1683-1986 of SEQ ID NO. 69 match that of a cloning vector sequence (see NCBI printout of "cloning vector psvbeta"). In cloning a nucleic acid sequence encoding after the promoter, it is unclear how to clone a coding region downstream of SEQ ID NO. 69 and arrive at translated protein. The cloning vector sequence in nucleotides 1683-1986 has ATG sites that are not in frame with the coding region of the first cloned sequence. As such, neither the specification nor the art provide guidance in using SEQ ID NO. 69.

As such, the claims are not enabled for their fullest breadth.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 22 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is drawn to a mammalian sequence that is an avian sequence. Mammals are not birds. As such, it is unclear how a mammalian promoter is a subset of bird promoters.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11,13, 16-21, 23, 24, 26-28, 31-39, 43, 72-74, 134, 135 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Brown and Mahuran, 1993, American Journal of Human Genetics, 53: 497-508, in view of Li and Li, 2001, International Congress Series, 1223: 3-15, Rossi et al., 1998, Nature Genetics, 20: 389-393, Kim et al., 1992, Molecular and Cellular Biology, 12: 3636-3643, Proia, 1988, PNAS, USA, 85: 1883-1887, Myerowitz et al., 1985, PNAS, USA, 82: 7830-7834, Patapoutian et al., WO 02/101045 A2, published December 19, 2002, Hobbs [online], 1997 [retrieved on 2008-03-02]. Retrieved from the Internet:< URL: http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?cmd=Retrieve&db=Nucleotide&list_uids=2329859&dopt=GenBank&WebEnv=0npmzO46M-ZDooSlRrzuukhPw99uI5bvKx98CayPdO_uLYe5w4_-6eC9cd-KucPViMuvowjZ0gwTJT%40256362576FC165A0_0107SID&WebEnvRq=1>, pages 1-3, Hennighausen and Fleckenstein, 1986, EMBO Journal, 5: 1367-1371, Kost et al., 1983, Nucleic Acids Research, 11: 8287-8301, Kistner et al., 1996, PNAS, USA, 93: 10933-10938, Sauer, 1998, Methods, 14: 381-392, Banerjee et al., 1994, The Journal of Biological Chemistry, 269: 4819-4826.

Brown and Mahuran teach that a cDNA clones of human HEXA, human HEXA with a Glu482 to Lys substitution, human HEXA with a Gly250 to Asp mutation, a human HEXA with a Gly269 to Ser mutation, human HEXB, human HEXB with a Gly301 to Ser substitution were cloned into various mammalian expression vectors (Brown and Mahuran, page 498, under "Vector Construction and Site-directed Mutagenesis"). Brown and Mahuran teach that when they co-transfected alpha(Gly269 to Ser) Hex and wild type beta Hex, heterodimer formation (i.e., HEX A) was less than that of the cells cotranfected with wild type alpha and beta Hex. 4-methylumbelliferone-beta-N-acetylglucosamine-6 sulfate (MUGS) was used to determine amount of heterodimer formation (Brown and Mahuran, page 499, under "Immunoselection Assay for Hex A, Hex B, and Hex S Activity" and page 501, under "In Vitro Expression of Heterodimeric Hex A"). With regard to promoters (e.g. see claim 3), Brown and Mahuran teach that promoters such as the SV40 late promoter and SV40 early promoter can be used. It is noted that MUGS is an artificial substrate used to measure GM2 catabolism (Li and Li, abstract). It is also noted that the SV40 promoter is a constitutive promoter (claim 17), see Rossi et al., legend of Figure 5.

While Brown and Mahuran teach cotransfection of human HEXA and HEXB into cells, they do not teach expressing HEXA and HEXB from one vector, using an IRES.

Kim et al., teach that a ribosomal internal entry site (IRES) is a cis-acting element that provides a site for internal binding of ribosomes and cap-independent translation. Kim et al. teach that the IRES provides a way by which to obtain temporally and

spatially coordinated expression of two different genes driven by a single promoter in a single cell (Kim et al., abstract).

All of the components of the claimed composition are known in Brown and Mahuran and Kim et al. The only difference is the combination of the single expression construct into one construct that expresses two transgenes. It would have been obvious to one having ordinary skill in the art to take Kim et al.'s teaching of using an IRES in an expression vector such that Hex A and Hex B can be expressed from one vector.

With regard claim 1 and 72 reciting the sequence having 70% identity to SEQ ID NO. 3 and SEQ ID NO. 1 a sequence search identified that SEQ ID NO. 3 had a 99.8% match with that of Prioa and SEQ ID NO. 1 had a 93.1% match with that of Myerowitz et al., the sequence used by Brown and Mahuran (see printout). In addition to this, Patapoutian et al. teach that making conservative changes (claims 13, 74) in proteins are known in the art. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given polypeptide. For example, multiple codons can encode arginine. In addition to these "silent variations," the art teaches that an artisan will recognize that individual substitutions, deletions, or additions which alter, add, or delete a single amino acid or a small percentage of amino acids in an encoded sequences are "conservatively modified variations" where the alterations result in the substitution of an amino acid with a chemically similar amino acid. As such, making conservative amino acid changes in HexA or HexB would have been obvious.

With regard to the claims being drawn to whether the HEXA and HEXB nucleic acid sequences are before or after the IRES (claims 2, 5, 7-9), this is a matter of design choice and an artisan would have been as likely to put HEXA before HEXB or HEXB before HEXA in a vector as Kim et al. teach that the IRES provides a way of expressing two genes driven by a single promoter.

With regard to the claims being drawn to using a second IRES (claim 10, 11) and using a reporter gene (claims 31, 32) it would have been obvious for an artisan to include a second IRES to drive expression of a reporter gene such as lacZ. Kim et al. used IRES and lacZ in their study and illustrate that lacZ can be used to show which cells were positive to the transgene construct.

With regard to the claims being drawn to a particular IRES (claim 16), the sequence was known at the time of filing Hobbs posted the sequence of pSIRES on NCBI. An artisan would have been as likely to use the IRES taught by Hobbs as that taught by Kim et al. as both nucleic acids provide the same function.

With regard to the claims being drawn to the use of constitutive promoters (claims 17-23) and that an artisan would have used other constitutively active promoters such as CMV and b-actin as they perform the same function as the SV40 promoter in terms of being constitutive promoters. With regard to using SEQ ID NO. 32, (CMV promoter), the sequence was known at the time of filing, see Hennighausen and Fleckenstein, Figure 2. In addition to this, SEQ ID NO. 26 (beta-actin) was known at the time of filing, see Kost et al.

With regard to the promoter being inducible (claim 24), Kistner et al. teach that an inducible promoter is a "genetic switch" that could be operated at will and would permit the control of individual gene activities quantitatively and reversibly in a temporal and spatial manner. The tetracycline (Tc)-controlled system for activation of transcription is one such example. Kistner et al. describe two types of inducible systems. The "reverse Tc-controlled transactivator" (rtTA) system uses doxycycline (dox) as an inducer of transcription and the "Tc-controlled-transactivator" (tTA) system uses Tc or dox to prevent transcription activation (Kistner, page 10933, 1st col., 2nd parag. to 2nd col., 1st parag., see also Figure 1). As such, it would have been obvious for an artisan to use an inducible promoter as it would provide an artisan with a way of controlling gene expression.

With regard to the claims being drawn to a reporter gene being flanked by recombinase sites (claims 31-34) or a termination site being flanked by recombinase sites (claims 35-38), the art teaches that the Cre-lox system is frequently used to remove nucleic acid sequences flanked by loxP sites. Sauer et al. teach that a target gene can be flanked by loxP sites and upon expression of Cre-recombinase, the nucleic acid sequence flanked by the loxP sites are removed by Cre-mediated recombination. These nucleic acid sequences include a stop cassette (Sauer, Figure 2) and a gene of interest (Sauer, Figure 3). It is noted that claim 36 is drawn to the transcription termination site oriented 5' to the promoter sequence. While Sauer and the specification (Figure 13, legend) discuss the stop cassette being between the promoter and the gene of interest, it is possible to place the stop cassette 5' of the promoter.

Given that expression constructs are circular, if an artisan follows the 5' end around the construct, eventually, the stop cassette, placed between the promoter and the gene of interest would be 5' to the promoter.

With regard to the composition producing HEXB, HEXA, or HEXS product (claims 26-28), Brown and Mahuran teach that the co-transfected cells expressed wild type HexA and HexB. These proteins would have made homo- and heterodimers of HEXB, HEXA, and HEXS.

With regard to the vector being stably integrated (claims 39, 43), Banerjee et al. teach that in addition to transiently transfecting cells with an expression construct, expression constructs can be stably integrated into a host's genome (Banerjee et al., page 4821, under "Stable Incorporation of beta-Hex, alpha- and beta-chain cDNA into Cos-7 Cells"). As such, integrating a transgene into the genome of a host cell is design choice and an artisan would have been as likely to stably integrate a transgene in a genome as to do a transient transfection.

Thus, the claims are obvious.

Claims 1, 4, 6, 39-42, 87, 90, 91 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Brown and Mahuran, 1993, American Journal of Human Genetics, 53: 497-508, in view of Li and Li, 2001, International Congress Series, 1223: 3-15, Kim et al., 1992, Molecular and Cellular Biology, 12: 3636-3643, Chavany and Jendoubi, 1998, Molecular Medicine Today, 4: 158-165, Schuette et al., 1999, Biol.

Chem. 380: 759-766, Litchtler et al., 1989, The Journal of Biological Chemistry, 264: 3072-3077, Klimatcheva et al., 1999, Frontiers in Bioscience, 4: d481-496.

As discussed above, the combined teachings of Brown and Mahuran, Li and Li, and Kim et al. provide guidance for an artisan to make an isolated nucleic acid wherein the nucleic acid comprises nucleic acid sequences encoding HEXA and HEXB operably linked to a ubiquitous promoter. While the combined teachings provide this guidance, they do not teach use of a neural-specific promoter and a lentiviral vector.

Chavany and Jendoubi teach that lipid accumulation resulting from defective ganglioside catabolism occurs predominantly in the organs where the respective lipid substrates are synthesized. As such, defective GM2 catabolism, which is most abundant in neurons, leads mainly to neuronal distortion and severe neurological degeneration (Chavany and Jendoubi, page 160 under "Pathology of the GM2 gangliosidoses"). As such, an artisan would want to substitute the constitutive promoter with a neural-specific one, such that expression of HexA and HexB would be localized in neuronal tissue. One such example is a NSE promoter (claim 88). With regard to using a skin-specific promoter (claims 90, 91), Schuette et al. teach that skin is also affected in Tay-Sachs and Sandhoff patients (Schuette et al., abstract). As such, an artisan would also want to substitute the constitutive promoter with a skin-specific one. It is noted that SEQ ID NO. 70 was known at the time of filing, see Lichtler et al., Figure 2.

With regard to using a lentiviral vector (claims 40-42), Chavany and Jendoubi teach that one problem of gene therapy is getting constructs past the blood brain

barrier. To circumvent this, viral vectors such as the herpes simplex virus (HSV) or adenovirus vectors can be used. Chavany and Jendoubi also teach that human immunodeficiency virus (HIV) can also be used to overcome the problem that retroviral vectors do not infect neurons. With regard to the claims being drawn to feline immunodeficiency virus (FIV), the art teaches that FIV vectors were used in gene therapy applications (Klimatcheva et al., page 482, 2nd col., 1st parag.) and it would have been as likely to use a FIV vector as an HIV one.

Thus, the claims are obvious.

Examiner's note: A search of SEQ ID NO. 1 appears to indicate that the sequence is free of the art. It is noted that the first 15 amino acid sequences of SEQ ID NO. 1 did not match any of the known human HexA sequences. When a BLAST search was performed on the first 15 amino acid sequences of SEQ ID NO. 1, the search result indicates that the sequence is the first 15 amino acids of goat HexA sequence (see printout). Nothing in the art appears to provide guidance for making this modification.

Conclusion

Claims 14, 138, 142 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 83 is allowable.

Claims 1-11, 13, 14, 16-43, 72-74, 87-91, 134, 135, are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file

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/Joanne Hama, Ph.D./
Examiner, Art Unit 1632